

Matching the Modules: Cortical Maps and Long-Range Intrinsic Connections in Visual Cortex during Development

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ABSTRACT: Visual cortical neurons exhibit a high degree of response selectivity and are grouped into small columns according to their response preferences. The columns are located at regularly spaced intervals covering the whole cortical representation of the visual field with a modular system of feature-selective neurons. The selectivity of these cells and their modular arrangement is thought to emerge from interactions in the network of specific intracortical and thalamocortical connections. Understanding the ontogenesis of this complex structure and contributions of intrinsic and extrinsic, experience-dependent mechanisms during cortical development can provide new insights into the way the visual cortex processes information about the environment. Available data about the development of connections and response

properties in the visual cortex suggest that maturation proceeds in two distinct steps. In the first phase, mechanisms inherent to the cortex establish a crude framework of interconnected neural modules which exhibit the basic but still immature traits of the adult state. Relevant mechanisms in this phase are assumed to consist of molecular cues and patterns of spontaneous neural activity in cortical and corticothalamic interconnections. In a second phase, the primordial layout becomes refined under the control of visual experience establishing a fine-tuned network of connections and mature response properties. © 1999 John Wiley & Sons, Inc. *J Neurobiol* 41: 10–17, 1999

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The highly specialized response properties of cortical neurons result from the elaborated anatomical and functional architecture of the neocortex in which the neurons are embedded. Within the primary visual cortex neurons with similar response properties are grouped in columns or modules that extend vertically through the cortical lamination. Long-range intrinsic axons reciprocally link columns of similar functional properties that are spaced at regular intervals. Therefore, functional properties and the architecture of connections are closely related. The evidence that both functional properties and anatomical architecture mature under the influence of visual experience and are

modifiable by manipulating experience raises the question to which extent the layout of visual representations in functional maps is based on genetic and epigenetic factors, respectively. In the following, we review data on the development of feature maps and intracortical circuitry focusing on the development of orientation selectivity in the visual cortex of cats and ferrets.

SPATIAL PROPERTIES OF ORIENTATION PREFERENCE MAPS IN PRIMARY VISUAL CORTEX

The preferred orientation of neurons in the cortex changes continuously in a plane tangential to the cortical lamination and preferences for the same ori-

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entation repeat at rather regular intervals (Hubel and Wiesel, 1962). Metabolic mapping techniques such as 2-deoxyglucose autoradiography (Sokoloff et al., 1977) suggested a two-dimensional arrangement of iso-orientation columns in parallel slabs or irregular blobs (Hubel et al., 1977; Albus, 1979; Singer, 1981; Löwel and Singer, 1987; Humphrey et al., 1980). The more comprehensive mapping technique based on optical imaging of intrinsic signals (Grinvald et al., 1986) revealed subsequently that the different orientation domains are not perfectly parallel to each other, but are arranged radially around singularities, at which the preferred orientations change rapidly (Bonhoeffer and Grinvald, 1991).

There is evidence that orientation selectivity at least in the adult mainly originates from the specific and precise alignment of thalamocortical connections onto layer IV neurons (Chapman et al., 1991; Reid and Alonso, 1995; Ferster et al., 1996), as originally suggested by Hubel and Wiesel (1962).

In addition to orientation preference, neurons exhibit preferences for either the ipsi- or the contralateral eye and form bandlike alternating ocular dominance columns (Hubel and Wiesel, 1965, 1972; Shatz et al., 1977). Within these columns, the neurons in layer IV which receive the eye-specific input from the thalamus exhibit the strongest eye preference. In normally reared cats, most of the neurons in supra- and infragranular layers are binocular with only a bias for one eye (Hubel and Wiesel, 1962). Earlier 2-deoxyglucose studies failed to reveal a relation between the maps of ocular dominance and orientation preference (monkeys: Hubel et al., 1978; cats: Löwel et al., 1988). However, recent investigations with optical imaging revealed consistent relations between the two columnar systems in both monkeys and cats as originally suggested by Hubel and Wiesel (1977). Orientation singularities were found to be located predominantly within the centers or peaks of ocular dominance columns and the trajectories of iso-orientation domains cross the borders between adjacent ocular dominance columns significantly more often at right angles than expected from an even distribution (Bartfeld and Grinvald, 1992; Obermayer and Blasdel, 1993; Crair et al., 1997; Hübener et al., 1997; Löwel et al., 1998).

INTRINSIC AND ENVIRONMENTAL INFLUENCES ON THE DEVELOPMENT OF ORIENTATION SELECTIVITY

In kitten visual cortex, the earliest neuronal responses to light flashes applied through the still closed eyelids

were recorded at the fourth postnatal day (PND4) (Huttenlocher, 1967). Orientation-selective responses were found to variable degrees as early as the eyes open around PND10 in cats (Hubel and Wiesel, 1963, Blakemore and Van Sluyters, 1975; Buisseret and Imbert, 1976; Albus and Wolf, 1984; Braastad and Heggelund, 1985; but see Barlow and Pettigrew, 1971; for a detailed review, see Fregnac and Imbert, 1984) and around PND23 in ferrets (Chapman and Stryker, 1993). A 2-deoxyglucose study provided evidence for a modular organization of orientation preference at PND21 in cats (Thompson et al., 1983), and recent optical imaging data demonstrated orientation preference maps in area 17 of cats as early as PND14 (Crair et al., 1998) and in area 17 of ferrets at PND33 (Chapman et al., 1996). Most studies agree that in cats the maturation of orientation selectivity occurs independently of visual experience within the first 3 weeks (Blakemore and VanSluyters, 1975; Buisseret and Imbert, 1976; Fregnac and Imbert, 1978; Mower et al., 1981). The quality of cortical maps improves over this period irrespective of whether kittens are normally reared or visually deprived (Goedecke et al., 1996; Crair et al., 1998).

This initial experience-independent formation of orientation maps is followed by a second developmental phase during which further maturation is influenced by visual experience. With normal vision, the overall proportion and responsiveness of orientation-selective neurons increase steadily until the sixth postnatal week in cats (for review, see Fregnac and Imbert, 1984) and the seventh postnatal week in ferrets (Chapman and Stryker, 1993). In cats, visual input is required beyond the third postnatal week for the maintenance and further elaboration of orientation-selective responses and the organization of neurons into iso-orientation domains. Deprivation from pattern vision in this second phase leads to a marked deterioration of the already established cellular response properties (for review, see Fregnac and Imbert, 1984; Henry et al., 1994) and orientation preference maps (Crair et al., 1998). However, the earliest maturing orientation-selective neurons which prefer vertical or horizontal contours, are located mainly in layer IV and driven through the contralateral eye (Blakemore and VanSluyters, 1975; Buisseret and Imbert, 1976; Fregnac and Imbert, 1978; Crair et al., 1998; ferrets: Chapman and Bonhoeffer, 1998), seem to resist visual deprivation (Leventhal and Hirsch, 1980; Buisseret et al., 1982; Thompson et al., 1983).

The development of functional properties can also be influenced by manipulating the nature of visual experience. The proportion of neurons displaying a certain orientation preference can be selectively in-

creased by exposing animals to an environment containing only contours of this very orientation (Hirsch and Spinelli, 1971; Blakemore and VanSlyuyters, 1975; Leventhal and Hirsch, 1975; Blasdel et al., 1977; Stryker et al., 1978; Flood and Coleman, 1979; Rauschecker and Singer, 1981; Singer, 1981; Sengpiel et al., 1998; for review, see Fregnac and Imbert, 1984; Henry et al., 1994). These changes in the distribution of preferred orientations appear to be due to a shift toward the experienced orientation in neurons whose initial tuning already allowed them to respond to that orientation. Neurons which are initially unable to respond to the experienced orientation maintain their original preference. Since only those stimuli which match the receptive field properties of the postsynaptic neuron effectively induce modifications, postsynaptic activation is presumably required for these changes to occur (Cynader and Mitchell, 1977; Rauschecker and Singer, 1979; Singer et al., 1981).

LONG-RANGE INTRINSIC CONNECTIONS

In principle, two types of intrinsic connections can be distinguished in the visual cortex: local connections confined to columns or the close neighborhood, and long-range connections between neurons located in different columns. The latter type of connections forms a reciprocal system of axon collaterals which arborize at regular distances of about 1 mm. Both physiological and anatomical evidence from several species indicates that this system preferentially links cortical columns with similar functional properties, e.g., the same orientation preference (Ts'o et al., 1986; Gilbert and Wiesel, 1989; Schwarz and Bolz, 1991; Hata et al., 1991; Malach et al., 1993, 1994; Bosking et al., 1997). Tangential connections between iso-orientation domains exhibit in addition an axial anisotropy, linking neurons with colinearly aligned receptive fields over longer distances than neurons preferring similar but not colinear orientations (Fitzpatrick, 1996; Schmidt et al., 1997a).

In the adult, long-range connections contribute to the generation of orientation and direction selectivity (Eysel et al., 1987, 1990), mediate the dynamic modulation of receptive field properties by stimuli presented outside the classical receptive field (for review, see Gilbert, 1998), and contribute to the synchronization of responses (for review, see Singer and Gray, 1995).

DEVELOPMENT OF LONG-RANGE INTRINSIC CONNECTIONS

In cat and ferret visual cortex, long-range intrinsic connections develop only postnatally, and they do so in two phases: First, a network of crudely clustered long-range connections forms between pyramidal neurons located mainly in supragranular layers. Subsequently, these crude clusters become refined and the total length of the reciprocal connections increases by 50–100%. This process of refinement and extension of tangential intrinsic connections appears to take 4–6 weeks in the cat (Luhmann et al., 1990; Callaway and Katz, 1990; Galuske and Singer, 1996) and 3 weeks in the ferret (Ruthazer and Stryker, 1996; Durack and Katz, 1996).

The initial clustering of tangential connections is likely to be independent of visual experience: First, crude clusters in both kittens and ferrets emerge before eye opening, around PND10 in cats (Luhmann et al., 1986; Callaway and Katz, 1990; Galuske and Singer, 1996) and around PND27 in ferrets (Durack and Katz, 1996; Ruthazer et al., 1996). Second, clustered intrinsic connections are present in animals binocularly deprived from birth (Luhmann et al., 1990; Callaway and Katz, 1991). Third, dark rearing (Luhmann et al., 1990) or blocking retinal activity (Ruthazer and Stryker, 1996) does not prevent the initial clustering, either. The only manipulation so far which prevents the clustering of tangential connections is the blockade of neuronal activity within the cortex (Ruthazer and Stryker, 1996). This suggests that the early patterning of these connections is achieved by intrinsic processes whereby self-generated activity in cortical or reciprocal corticothalamic circuits might play an important role.

Morphological studies indicate that the earliest long-range intrinsic connections do not originate from neurons in the cortical plate, the progenitor of the prospective cortical layers II–VI, but from cells in cortical layer I and the subplate (Galuske and Singer, 1996). These cells are among the first to be generated and to reach their target position, but most of them are transient and disappear again (Luskin and Shatz, 1985). The neurons in the subplate, a cortical compartment below layer VI, have been shown to be decisive for cortical development. They gate and guide the ingrowth of thalamic afferents (Ghosh and Shatz, 1994), constituting the first target for LGN afferents and projecting back to the thalamus (for review, see Shatz et al., 1990). In analogy, the connections among these early transient cells in the subplate and in layer I could serve as a scaffold for the

subsequent development of tangential connections originating from the later maturing pyramidal cells, e.g., by generating periodically modulated activity patterns.

The second phase of the development of long-range intrinsic connections is influenced by pattern vision. Both the refinement of the connections that transforms the crudely clustered network into the highly selective mature state (Luhmann et al., 1990, Callaway and Katz, 1991; but see Lübke and Albus, 1992) and the elongation of connections up to 8 mm (Luhmann et al., 1990) are prevented by binocular visual deprivation. The refinement of the connections is mainly based on the elimination of axon collaterals to possibly inappropriate locations (Callaway and Katz, 1991). It is an interesting unresolved question whether these eliminated axons had already contacted target cells before elimination, and if so, whether they became inappropriate owing to maturation-related alterations in the functional properties of the interacting cells. One reason for such alterations could be cortical growth: The surface of the primary visual cortex increases by at least 40% between the third and sixth postnatal week in cats (Duffy et al., 1998; Rathjen et al., 1998). This enlargement is thought to be based on the elaboration of dendritic and axonal elements and the addition of myelin, neurogenesis, and neuronal migration having come to an end by that time (Luskin and Shatz, 1985). However, despite this enlargement of the cortical surface, the periodicity of interconnected modules does not change significantly between the end of the second postnatal week and adulthood (Galuske and Singer, 1996; Rathjen et al., 1998). This implies that the number of modules connected by clustered intrinsic connections increases. Since no new cells are formed, division of existing clusters appears to be the most likely scenario. Irrespective of the mechanism for the generation of new clusters, it seems inevitable that clusters shift their location to keep their spacing constant during cortical growth. This, in turn, could be associated with a change in the neuron's orientation preference and necessitate rearrangement of some of the already established tangential connections.

RELATION BETWEEN CORTICAL MAPS AND LONG-RANGE INTRINSIC CONNECTIONS DURING DEVELOPMENT

Although not studied longitudinally in the same animal, data from cat and ferret visual cortex suggest that the early clustering of intrinsic connections (Callaway

and Katz, 1990; Luhmann et al., 1990, Galuske and Singer, 1996, Ruthazer and Stryker, 1996, Durack and Katz, 1996) precedes the formation of orientation preference maps by a few days (Crair et al., 1998; Chapman et al., 1996). However, a small proportion of orientation selective neurons has been observed around or slightly before the time of the initial clustering of tangential connections in the cat (Hubel and Wiesel, 1965; Blakemore and VanSluyters, 1975) and ferret (Chapman and Stryker, 1993). There is thus a close temporal correlation between the clustering of tangential connections and the appearance of orientation-selective responses.

Both early orientation selectivity and initial clustering of connections are likely to be shaped by intracortical interactions. Self-generated patterned waves of retinal activity (Meister et al., 1991) do not appear to be crucial (Chapman et al., 1993; Weliky and Katz, 1996; Ruthazer et al., 1996). Hence, the initial symmetry breaking in the network of horizontal connections could be due to intracortically generated activity patterns. Whether the response properties of the early maturing orientation selective neurons in layer IV are also generated by the influence of such activity patterns on the cortical circuitry is unknown. Alternatively, the response properties of these neurons could be predetermined by local interactions, e.g. anisotropic inhibition, and these in turn could influence the structure of spontaneous activity. Both scenarios would render cortical cells selective for particular input constellations, e.g., for input patterns generated by elongated contours once visual input is available. This initial response bias could then promote the selection of the appropriate array of thalamic input connections. Support for this hypothesis comes from several lines of evidence: First, in the course of reversed monocular deprivation cortical neurons become disconnected from the initially deprived eye (Antonini and Stryker, 1994), and upon reversal get reconnected to this eye. During reversal, cells pass through a phase in which they are unresponsive to stimulation of either eye, but upon reconnection to the newly opened eye they express the same orientation preferences as before (Mioche and Singer, 1989). Second, the orientation maps remain unchanged during reversal of monocular deprivation (Kim and Bonhoeffer, 1994; Antonini et al., 1998). Third, orientation maps are similar for the two eyes even if the two eyes never received common visual experience (Goedde and Bonhoeffer, 1996). These results suggest that the orientation preference of cortical neurons is determined by intracortical interactions and that the selection of the specific alignment of thalamic afferents (Chapman et al., 1991) which supports the re-

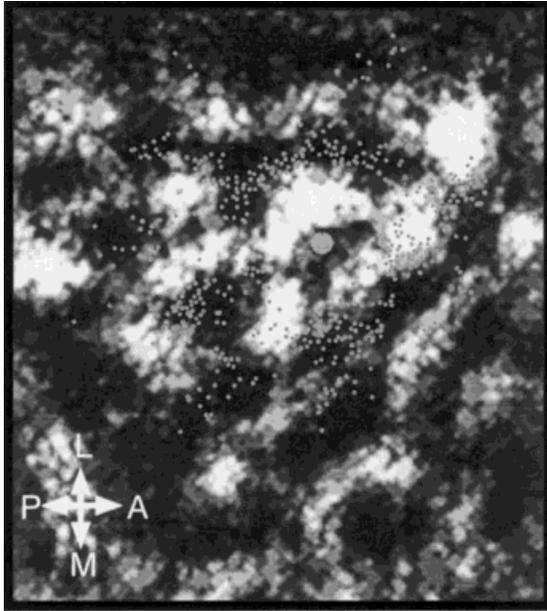


Figure 1 Topographic relations between intrinsic horizontal connections and monocular orientation domains (dark columns) in area 17 of a squinting cat (Schmidt et al., 1997b). A retrograde tracer (green fluorescent beads) was injected in a left eye orientation domain preferring 45° (thick dot, light gray) and iso-orientation domains were labeled by 2-deoxyglucose during monocular stimulation of the left eye with moving oblique bars (45°). A detail of the autoradiograph from a flat-mount section of the unfolded left hemisphere was superimposed with the distribution of retrogradely labeled neurons (small dots, light gray) that have long-range connections to the injection site. Note the close correspondence of green-labeled neurons and dark-labeled iso-orientation domains. Scale bar = 1 mm. A = anterior; L = lateral; P = posterior; M = medial.

spective preferences is achieved through an activity-dependent process. As proposed previously (Rauschecker and Singer, 1981), a Hebbian mechanism evaluating the contingency of pre- and postsynaptic firing could ensure that selection of reconnecting thalamic afferents occurs according to the cortically determined orientation preferences of the respective target cells.

Even after eye opening, orientation tuning and the selectivity of intrinsic connections continue to improve independently of visual experience (Blakemore and VanSluyters, 1975; Buisseret and Imbert, 1976; Fregnac and Imbert, 1978; Crair et al., 1998; Callaway and Katz, 1991), suggesting continued prevalence of the intrinsic specification processes. Such a prolongation of experience-independent development beyond eye opening could serve to prevent substantial activity-dependent remodeling before the sensory pe-

riphery and the motor control of the eyes have matured sufficiently.

In cats, visual experience influences the further maturation of orientation selectivity and the refinement of intrinsic connections beyond the beginning of the fourth postnatal week. At this stage, binocular deprivation affects both maps and connections, suggesting that visual experience serves to consolidate the already formed connections and to specify the still proliferating connections according to functional criteria. This process may also contribute to the reorganization of circuits associated with the implementation of new columns during cortical growth. If experience indeed serves to guide this reorganization process and to integrate newly formed connections into the already existing network, this could explain why the initially well-expressed maps deteriorate with long-term binocular deprivation.

Support for the hypothesis that the primordial orientation map is established by an experience-independent process and that the alignment of thalamic afferents is the result of a secondary, experience-dependent selection process comes from squinting animals. Because their visual axes are deviating, the input from the two eyes is permanently decorrelated, abolishing convergence onto common target cells and leading to a maximal segregation of thalamocortical afferents into ocular dominance territories (Shatz et al., 1977; Löwel and Singer, 1993). In this case, clustered tangential connections which normally connect neurons driven from either eye avoid interconnecting territories of different ocularity (Löwel and Singer, 1992). Despite this nearly complete eye-specific segregation of thalamic inputs and intracortical connections, iso-orientation domains were found to be continuous across territories of different ocularity (Löwel et al., 1998) as in normal animals (Hübener et al., 1997). Moreover, horizontal connections within the respective eye-specific subcompartments link iso-orientation domains as selectively as in normal animals (Schmidt et al., 1997b). Taken together, these findings are consistent with the view that (a) the formation of the orientation map precedes the selection of thalamic input and is resistant to rearrangements of thalamic afferents, (b) the susceptibility of horizontal connections to experience-dependent selection persists beyond the phase during which the orientation map stabilizes, and (c) orientation selectivity, once established, is maintained by local, intracolumnar, and/or short-range intercolumnar interactions since sequence regularity of orientation preference is maintained across the domains of different ocularities that are no longer connected by long-range tangential fibers.

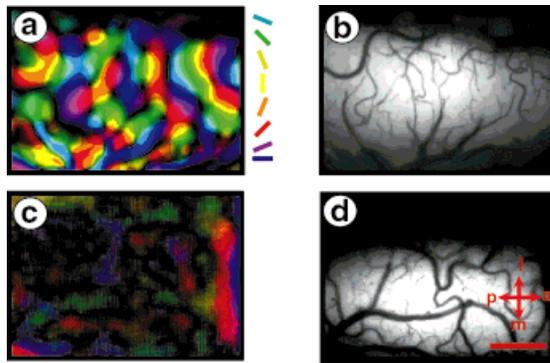


Figure 2 Influence of visual experience on the maturation of orientation maps (Galuske, unpublished observations). (a,c) Polar maps from optically recorded orientation maps in cat visual cortex. These maps result from vectorial summation of four different binocular single orientation maps (0° , 45° , 90° , and 135°). The angle of the resulting vector is color coded according to the scheme shown on the right edge of (a). In addition, the orientation tuning is indicated by the brightness of the respective pixels; bright colors indicate a narrow tuning, and dark colors a broad tuning. Note the well-tuned orientation domains in the map recorded from a normally reared adult animal (a). In a binocularly deprived adult animal (c) the pixels are poorly tuned, as indicated by the preponderance of dark colors. Moreover, orientation domains are not well segregated and variable in size. Video images of the recorded regions are shown in the normal (b) and the deprived animal (d). Scale bar = 1 mm. Abbreviations as in Figure 1.

In summary, the early development of the orientation map appears to be independent of retinal input and is likely to be based on intrinsic interactions that also support the clustering of tangential connections. This protonetwork could serve as a scaffold for the later, experience-dependent refinement of both thalamo-cortical and intracortical connections. The role of experience could be to make thalamic inputs congruent with the internally specified response properties of cortical neurons and to refine and validate intracortical connections according to functional criteria.

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